

LEH-35B-98
U.S. Ser. No. 09/493,891

REMARKS

Following entry of the present amendment, Claims 3, 5-9, and 16-23 remain in the application for consideration. Claims 3 and 5-8 have been amended and Claim 15 has been canceled without prejudice to or disclaimer of the subject matter therein. The amendments and cancellation were made notwithstanding the Applicants' belief that the canceled claims would have been allowable, and without acquiescing to any of the Examiner's arguments, and without waiving the right to prosecute in the future the canceled (or similar) claims in another application, for the purpose of furthering the Applicants' business goals and expediting the patent application process in a manner consistent with the PTO's Patent Business Goals (PBG).¹

Claim 3 has been amended to more clearly define the invention where the polysaccharide is specified, Claim 5 has been amended to more clearly define the solvent, and Claims 6-8 have been amended to more clearly define particular embodiments of the invention. Support for these amendments can be found throughout the specification, as for example, on page 6, lines 20-22. New Claims 16-23 have been added to claim embodiments that Applicants' have a right to claim; support for these claims is found throughout the specification, as for example, page 5, lines 12-17, and page 13, lines 11-18.

In the Final Office Action dated October 20, 2004, the Examiner made a number of objections and rejections. For clarity, the objections and rejections at issue are set forth by number in the order they are herein addressed:

1. Claims 3, 5, and 15 are rejected under 35 USC 112, first paragraph, as failing to comply with the written description requirement;
2. Claim 9 is rejected under 35 USC 102(b) as anticipated by Heindel (Bioconjugate Chem., 1994);
3. Claim 9 is rejected under 35 USC 102(b) as anticipated by Akanuma et al. (J. Biochem., 1978);
4. Claim 9 is rejected under 35 USC 102(a) as anticipated by Martey et al. (CAPLUS abstract 1998: 529836, 1998);

¹ 65 Fed. Reg. 54603 (September 8, 2000).

LEH-35B-98
U.S. Ser. No. 09/493,891

5. Claims 3 and 9, and newly added Claim 15, are rejected under 35 USC 103(a) as obvious over Akanuma et al. (J. Biochem., 1978);
6. Claims 3, 5, 6, and 9, and newly added Claim 15, are rejected under 35 USC 103(a) as obvious over Heindel (Bioconjugate Chem., 1994) and Akanuma et al. (J. Biochem., 1978);
7. Claims 3 and 5-9, and newly added Claim 15, are rejected under 35 USC 103(a) as obvious over Heindel (Bioconjugate Chem., 1994) and Akanuma et al. (J. Biochem., 1978) in further view of Mill et al. (US Pat No 4,003,792); and
8. Claims 3 and 15 are rejected under 35 USC 103(a) as obvious over Heindel (Bioconjugate Chem., 1994) and Hall et al. (US Pat No 4,424,346).

These actions are addressed below in the order listed above.

1. Claims 3, 5, and 15 are sufficiently described.

The Examiner rejected Claims 3, 5, and 15 under 35 USC 112, first paragraph, as failing to comply with the written description requirement (Office Action, page 2). The Examiner did not find support for the amendment to Claim 3 to require dehydration "for a period of greater than 5 hours."

However, as Claim 15 has been canceled², the rejection as to this claim is moot. Claim 3 has been amended to delete the phrase "for a period of greater than 5 hours," so the basis of this rejection is also moot. Because Claim 5 depends from Claim 3, the rejection of this claim is now also moot. Therefore, Applicants respectfully request the withdrawal of this rejection of the claims.

2. Claim 9 is not anticipated by Heindel.

The Examiner maintained the rejection of Claim 9 under 35 USC 102(b) as anticipated by Heindel (Bioconjugate Chem., 1994) (Office Action, page 2). The Examiner asserted that

² Claim 15 was canceled, notwithstanding the Applicants' belief that this claim would have been allowable, without acquiescing to any of the Examiner's arguments, and without waiving the right to prosecute the canceled (or similar) claim in another application, for the purpose of furthering the Applicants' business goals and expediting the patent application process.

LEH-35B-98
U.S. Ser. No. 09/493,891

Applicant amended the process to distinguish it from that disclosed in the reference, but failed to indicate how the product formed differs from the product-by-process of Claim 9.

Applicants note that Claim 3 has been amended to recite polysaccharide carboxylic acids. As these acids are not described in Heindel, the resulting products as claimed in Claim 9 are also not described in Heindel. Therefore, Claim 9 is not anticipated by Heindel, and Applicants respectfully request withdrawal of this rejection.

3. Claim 9 is not anticipated by Akanuma.

The Examiner maintained the rejection of Claim 9 under 35 USC 102(b) as anticipated by Akanuma et al. (J. Biochem., 1978) (Office Action, page 3). In the first Office Action, the Examiner asserts that Akanuma discloses the preparation of carboxymethyl dextran lactone from CM-dextran and CM-cellulose, and that the product appears to be otherwise identical.

Applicants first note that Akanuma describes lactone formation from CM-Sephadex in Step I (page 1358, right-hand column), and refers to "Observations on the Dextran Beads of Step I" as directed to the treatment of CM-Sephadex (paragraph bridging page 1359-1360). Thus, CM-Sephadex is made up of dextran beads. Although Akanuma states that CM-cellulose was also converted to its hydrazide derivative, Akanuma does not provide any confirmation of lactone formation from CM-cellulose.

Applicants note that Claim 3 has been amended to recite polysaccharide carboxylic acids. Because the lactone products of these acids are not described in Akanuma, the resulting products of Claim 9 are also not described in Akanuma. Therefore, Claim 9 is not anticipated by Akanuma, and Applicants respectfully request withdrawal of this rejection of Claim 9.

4. Claim 9 is not anticipated by Martey.

The Examiner maintained the rejection of Claim 9 under 35 USC 102(a) as anticipated by Martey et al. (CAPLUS abstract 1998: 529836, 1998) (Office Action, pages 3-4). In the first Office Action, the Examiner asserts that Martey discloses the dehydration of carboxymethylated dextran and cellulose to prepare a lactone product, but is silent on the identity of the solvent used in the process, and that the product appears to be otherwise identical to that claimed.

Submission with RCE
Page 8 of 15

LEH-33B-98
U.S. Ser. No. 09/493,891

However, in order to anticipate, a reference must be enabling. (MPEP 2121.01: "The disclosure in an assertedly anticipating reference must provide an **enabling disclosure** of the desired subject matter; mere naming or description of the subject matter is insufficient, if it cannot be produced without undue experimentation." *Elan Pharm., Inc. v. Mayo Foundation for Medical and Education Research*, 346 F.3d 1051, 1054, 68 USPQ2d 1373, 1376 (Fed. Cir. 2003)"; emphases added). Although Martey states that "it is possible to generate a reactive lactone by thermally-induced intramol. dehydration" from carboxymethylated dextran and cellulose, the reaction conditions are not described. From simply reading the abstract, one of ordinary skill in the art could not synthesize the named lactones. Therefore, this abstract does not teach how to make the claimed products, and thus does not enable to claimed subject matter. Because it is not an enabling disclosure, Martey does not anticipate Claim 9.

For these reasons, Applicants respectfully request the withdrawal of this rejection of the claim.

5. **Claims 3, 9, and 15 are not obvious over Akanuma.**

The Examiner maintained the rejection of Claims 3 and 9, and rejected newly added Claim 15, under 35 USC 103(a) as obvious over Akanuma et al. (J. Biochem., 1978) (Office Action, pages 4-5). The Examiner previously asserted that "Akanuma teaches as set forth above," which is allegedly that "Akanuma discloses the preparation of carboxymethyl dextran lactone by thermal dehydration of CM-dextran and CM-cellulose" but that "Akanuma is silent on whether or not the solvent used in this process is anhydrous" (emphases added).

However, as Claim 15 has been canceled³, the rejection as to this claim is moot.

Three basic criteria must be met to establish a *prima facie* case of obviousness (MPEP 2143). First, there must be some suggestion or motivation, either in the reference itself or in the knowledge generally available to one of ordinary skill in the art, to modify the reference. Second, there must be a reasonable expectation of success. Finally, the prior art reference must teach or suggest all the claim limitations. The Examiner has not met even one of these criteria.

³ Claim 15 was canceled, notwithstanding the Applicants' belief that this claim would have been allowable, without acquiescing to any of the Examiner's arguments, and without waiving the right to prosecute the canceled (or similar) claim in another application, for the purpose of furthering the Applicants' business goals and expediting the patent application process.

LEH-35B-93
U.S. Ser. No. 09/493,891

In contrast to the Examiner's assertions, Akanuma does not teach thermal dehydration of CM-dextran and CM-cellulose. Instead, Akanuma describes lactone formation by swelling the H-form of CM-Sephadex beads in dimethylformamide, adding DCC to the suspension (or thionylchloride and phosphorous pentachloride in its place), and then incubating the reaction overnight at room temperature (page 1358, second column). Thus, there is no heating step. Moreover, DCC, thionylchloride, and phosphorous pentachloride are powerful dehydrating chemicals. So the dehydration reaction described by Akanuma occurs chemically, and not thermally. Furthermore, the Examiner admits that Akanuma is silent on whether or not the solvent used in this process is anhydrous. Thus, the Examiner has failed to meet the third criteria that the prior art reference teach or suggest all of the claim limitations.

The Examiner has also failed to meet the first criteria, which is motivation or suggestion to modify the reference. The Examiner asserts that it would have been obvious to have used an anhydrous solvent, as "[t]he lactonization process produces, [sic] so the artisan would be motivated to minimize water in the starting material to move the equilibrium in favor of the products." The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggest the desirability of the combination or modification (MPEP 2143.01, citing to *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990)). Moreover, the fact that the claimed invention is within the capabilities of one of ordinary skill in the art is not sufficient by itself to establish *prima facie* obviousness (MPEP 2143.01, citing to *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App & Inter. 1993)). What exactly is the motivation to modify the Akanuma process? The claimed invention is directed to solving a problem resulting from a process such as is described by Akanuma: Use of chemical dehydration leaves undesirable residues in a resulting lactone product. Absent the realization that this result IS a problem, there is no motivation to "solve" it. The realization of this problem forms the foundation of the claimed invention; thus, if any motivation exists to modify the reference (which none does), it would be provided ONLY by the inventors in the specification. The Examiner is relying upon the specification to provide the proffered motivation, which is impermissible hindsight.

Submission with RCE
Page 10 of 15

LEH-35B-98
U.S. Ser. No. 09/493,891

Finally, the Examiner has also not met the second criteria. Even if one were motivated to use an anhydrous solvent (which is not the case), where is the expectation of success in the absence of **heating** the reaction?

Therefore, because the Examiner has failed to meet even one criterion, much less all three, to establish a *prima facie* case of obviousness, the cited reference does not make the claimed invention obvious. The Applicants thus respectfully request the withdrawal of this rejection of the claims.

6. Claims 3, 5, 6, 9, and 15 are not obvious over Heindel and Akanuma.

The Examiner maintained the rejection of Claims 3, 5, 6, and 9, and rejected newly added Claim 15, under 35 USC 103(a) as obvious over Heindel (Bioconjugate Chem., 1994) and Akanuma et al. (J. Biochem., 1978) (Office Action, page 5). The Examiner previously asserted that "Heindel teaches as set forth above," in that the reference allegedly "discloses the preparation of carboxymethyl dextran lactone by thermal dehydration of carboxymethyl dextran in an anhydrous, non-nucleophilic solvent (toluene, xylenes, diglyme, or acetomitrile)." The Examiner currently asserts that "Akanuma had demonstrated that CM-cellulose is capable of undergoing lactonization," and that one of ordinary skill "would be aware of possible variability reactivity among polysaccharides."

As Claim 15 has been canceled⁴, the rejection as to this claim is moot.

With respect to claims 3, 5, 6, and 9, the Examiner has once again not met even one criterion to establish a *prima facie* case of obviousness. An alleged awareness "of possible variability in reactivity among polysaccharides" is not a motivation to combine the two cited references. As Applicants noted above, Akanuma does not provide any confirmation of lactone formation from CM-cellulose. Moreover, where is the expectation of success from combining the two references? CM-cellulose is a very different molecule from CM-dextran, as Applicants pointed out in their Response to the first Office Action. For example, dextran is known to be the most flexible and elastic substance when compared to cellulose and it is virtually unique among

⁴ Claim 15 was canceled, notwithstanding the Applicants' belief that this claim would have been allowable, without acquiescing to any of the Examiner's arguments, and without waiving the right to prosecute the canceled (or similar) claim in another application, for the purpose of furthering the Applicants' business goals and expediting the patent application process.

LEH-35B-98
U.S. Ser. No. 09/493,891

polysaccharides in that it is very water soluble. These molecular differences also extend to the carboxymethyl derivatives. Thus, a report that a lactone is prepared from a dextran polysaccharide does not provide any expectation of success that a lactone can be prepared from a cellulose polysaccharide by the same procedure. In fact, the Applicants noted in their previous Response that the reaction conditions for dextran did not work for other polysaccharides. When considered with hindsight, this is believed to be due to the greater flexibility of dextan, which allows "closing" or lactone formation to occur at a lower temperature. Nor does an unconfirmed report that a lactone can be prepared by one procedure (chemically) from CM-cellulose provide any expectation of success that a lactone could be prepared from the same starting material by a different procedure (thermally). Finally, even a combination of the two references does not teach every element of the claims, which includes providing the polysaccharide as finely-powdered.

For these reasons, the combination of the two references do not make Claims 3, 5, 6, and 9 obvious, and Applicants respectfully request withdrawal of this rejection of these claims.

7. Claims 3, 5-9, and 15 are not obvious over Heindel and Akanuma in view of Mill.

The Examiner maintained the rejection of Claims 3 and 5-9, and rejected newly added Claim 15, under 35 USC 103(a) as obvious over Heindel (Bioconjugate Chem., 1994) and Akanuma et al. (J. Biochem., 1978) in further view of Mill et al. (US Pat No 4,003,792) (Office Action, pages 5-6). The Examiner previously asserted that "Heindel and Akanuma teach as set forth above," and that "Mills teaches that a wide variety of carboxylic acid polysaccharides, such as pectin, have utility in preparing polysaccharide bioconjugates," and therefore it would have been obvious "to lactonize any biocompatible carboxylic polysaccharide using the Heindel process for their art-disclosed utility in the preparation of bioconjugates."

The Applicants first note that because Claim 15 has been canceled⁵, the rejection as to this claim is moot.

⁵ Claim 15 was canceled, notwithstanding the Applicants' belief that this claim would have been allowable, without acquiescing to any of the Examiner's arguments, and without waiving the right to prosecute the canceled (or similar) claim in another application, for the purpose of furthering the Applicants' business goals and expediting the patent application process.

LEH-35B-98
U.S. Ser. No. 09/493,891

The Applicants next note that even if Mills does teach what the Examiner asserts, that does not mean that it teaches a method for the synthesis of a lactone of pectin where the solvent is toluene, as is claimed in Claim 7. Nor do the other two cited references teach this method, and the Examiner does not assert that they do. Therefore, this combination of references does not teach or even suggest all of the claim limitations. For these reasons alone, the Examiner has not met the criteria to establish a *prima facie* case of obviousness for Claim 7, and therefore the cited references do not make Claim 7 obvious. Therefore, Applicants respectfully request the withdrawal of this rejection of Claim 7.

The Examiner also does not demonstrate how the cited combination of references provides any expectation of success to "lactonize any biocompatible carboxylic polysaccharide using the Heindel process." Finally, the Examiner's assertion that "it would have been obvious" to combine the references is conclusory, and does not provide the requisite motivation to combine the cited references. Thus, the Examiner has failed to establish a *prima facie* case of obviousness for Claims 3, 5, 6 and 9 (as well as Claim 7), and for these reasons, the combined references do not these claims obvious. Therefore, Applicants respectfully request that the rejection of these claims also be withdrawn.

8. Claims 3 and 15 are not obvious over Heindel and Hall.

The Examiner had newly rejected Claims 3 and 15 under 35 USC 103(a) as obvious over Heindel (Bioconjugate Chem., 1994) and Hall et al. (US Pat No 4,424,346) (Office Action, pages 6-7). The Examiner asserts that Hall teaches the preparation of conjugates of chitosan derivatives, including N-carboxymethyl chitosan, and that therefore it would have been obvious "to use the method taught by Heindel to prepare a chitosan lactone," and that one "would reasonably expect success in using this method with a chitosan substrate."

First, because Claim 15 has been canceled⁶, the rejection as to this claim is moot.

Next, even if Mills does teach what the Examiner asserts, that does not mean that it teaches a method for the synthesis of a lactone of polysaccharide, as is claimed in Claim 3. Nor

⁶ Claim 15 was canceled, notwithstanding the Applicants' belief that this claim would have been allowable, without acquiescing to any of the Examiner's arguments, and without waiving the right to prosecute the canceled (or similar) claim in another application, for the purpose of furthering the Applicants' business goals and expediting the patent application process.

LEH-358-98
U.S. Ser. No. 09/495,891

does the Examiner assert that it does. Once again, the Examiner provides as a motivation for combining Hall with Heindel that it "would have been obvious" to do so. Such a statement, without more, is simply a conclusion. In establishing obviousness, "either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references" (MPEP 2141, citing *Ex parte Clapp*, 227 USPQ 972, 973, (Bd. Pat. App. & Interf. 1985), emphases added). The Examiner's conclusory statement is not a convincing line of reasoning.

Next, the statement that one "would reasonably expect success," without more, is also merely a conclusion, and does not provide any reason or basis as to why success would be expected.

Finally, even the combination of references does not teach all of the elements of Claim 3, which includes provision of the polysaccharide carboxylic acids as finely powdered.

Therefore, the Examiner has failed to meet the criteria to establish a *prima facie* case of obviousness, and the combination of the two references does not make Claim 3 obvious. For this reason, Applicants request the withdrawal of the rejection of this claim.

Submission with RCE
Page 14 of 15

LEH-358-98
U.S. Ser. No. 09/493,891

CONCLUSION

In view of the claim cancellations and amendments described in above, and the ~~Remarks~~ presented above, Applicants now submit that the application is in condition for allowance, ~~and~~ respectfully request issuance of a timely Notice of Allowance.

If the Examiner has any questions or feels that a discussion with Applicants' representative would expedite prosecution, the Examiner is invited and encouraged to contact Applicants' undersigned representative at the telephone number listed below.

Respectfully submitted,

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Submission with RCE
Page 15 of 15